REMARKS

Claims 12-27 are pending. Claims 12-15 and 23-27 are under examination. Claims 12-15 have been amended. Claims 12 and 15 have been amended to remove the narrower range element "including a human." This element now appears as new dependent claim 28. Amended claims 13 and 14 put the Markush groupings in the grammatical style requested by the Examiner. Claims 14 and 15 have been further amended to remove the relative terms "other" and "another." Claim 23 was previously cancelled. Accordingly, these amendments do not raise an issue of new matter and entry thereof is respectfully requested.

Claim Objections

Claims 13 and 14 are objected to as allegedly being written in improper Markush format. Claims 13 and 14 are amended herein to comply with the Examiner's objection. Applicants respectfully request withdrawal of this objection.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner's rejection of claims 12, 14, and 23-27 under 35 U.S.C. 112, first paragraph as allegedly lacking written description for the genus encompassed by "a sodium channel-inhibiting substance" or "analogs," as it refers to the disclosed chemical species, is respectfully traversed. (Office Action at page 2-5)

The Examiner concedes that the disclosure of tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide, and metixen are all suitable examples of "sodium-channel inhibiting substances" which meet the written description and enablement requirements. (Office Action at page 3, lines 1-4) However, the Examiner alleges that the term "a sodium channel-inhibiting substance" includes "antagonists and partial antagonists of sodium channel including sodium/hydrogen exchangers, sodium-glucose transporters, sodium/myoinositol cotransporter, Na+/I- symporter, sodium/potassium/calcium exchanger, Na+/K+/Cl- cotransporter and etc…or 'analogs' which only correspond in some undefined way to specifically instantly disclosed chemicals."

Applicants respectfully point out that the Examiner is applying a definition of "sodium channel" that does not appear consistent with common usage by those skilled in the art. For example, the National Library of Medicine Medical Subject Headings index organized by the National Institute of Health has a completely separate classification for "sodium channels" compared to the various symporters, cotransporters, and exchangers enumerated by the Examiner. "Sodium channels" are listed under [D12.776.157.530.400.875] and are defined therein as "cell membrane glycoproteins selective for sodium ions. Fast sodium current is associated with the action potential in neural membranes." (http://www.nlm.nih.gov/cgi/mesh/2008/MB_cgi?mode=&term=Sodium+Channels) None of the enumerated symporters, cotransporters, and exchangers share this selectivity for the transport of sodium ion. Furthermore, "sodium channels" belong to the broader classification of Ion Channels [D12.776.157.530.400] whereas the various symporters, cotransporter, and exchangers belong to the classifications of Ion Pumps [D12.776.157.530.450] or Monosaccharide Transport Proteins [D12.776.157.530.500], for example. Indeed, ion pumps move ions across the cell membrane against their concentration gradient, whereas with ion channels, the ions move through passive transport.

With respect to the term "analog," Applicants wish to clarify that this does not appear as a claim element in base claim 12, although claims 14-15 and the specification do refer to tolperisone analogues specifically. Tolperisone analogues are described in the specification , for example, at page 3, lines, 31-37, page 4, lines10-14, and page 6, line 11. Applicants submit that because tolperisone analogues were well-known at the time of filing of the application, one skilled in the art would understand the scope of the claims as it relates to this compound.

Moreover, Applicants submit herewith U.S. Patent No. 4,181,803 (Morita et al., Exhibit A) and U.S. Patent No. 4,528,299 (Uno et al., Exhibit B) which exemplify the level of knowledge in the art regarding tolperisone analogues at the time the application was filed. Morita et al. teach, for example, at column 2, line 63 through column 3, line 2, 4'-tolperisone analogs wherein the 4' methyl group is replaced by ethyl, *n*-propyl, or *i*-propyl. See also the accompanying data in Tables 1 and 2 at columns 3-4. Uno et al. teach a number of tolperisone analogs, for example, in Table 1, columns 3-4, that were known in the art (compounds 2-5) as well as novel analogs (compounds 6-8).

Because the Examiner concedes that the disclosure of tolperisone, eperisone, silperisone, riluzole, propafenone, lidocain, flecainide, and metixen are all suitable examples of "sodium-channel inhibiting substances" which meet the written description and enablement requirements, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner's rejection of claims 12-15 and 24-27 under 35 U.S.C. §112, second paragraph for failing to particularly point out and distinctly claim the subject matter is respectfully traversed. (Office Action at pages 5-6)

The Examiner alleges that claims 14 and 15 lack clarity due to the alleged ambiguity of the terms "other tolperisone analogs" or "another tolperisone analog." With respect to "other" or "another" these terms have been removed by way of amendment rendering the issue moot.

With respect to the term "including human," this phrase has been removed. The invention includes human subjects and Applicants have redrafted this element in the form of a new dependent claim. Accordingly, this redrafting renders this ground of rejection moot.

Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §103

The rejection of claim 12-13 and 23-27 under 35 U.S.C. §103(a) as allegedly being unpatentable over Rundfeldt et al. (U.S. 6,227,900) in view of Cai et al. (U.S. 6,281,211) and in further view of applicant's alleged admitted prior art of record (page 1, line 25- page 4, line 3) is respectfully traversed for the reasons of record and the following additional remarks.

The Examiner alleges that Cai teaches the "routine knowledge" in using sodium ion channel blockers to treat neuropathic pain. The Examiner also cites the background portion of the present specification with respect to the use of sodium ion channel blockers to normalize or maintain muscle tone (spasticity). Finally, the Examiner cites Rundfeldt for teaching the use of retigabine for treating neuropathic pain. The Examiner then asserts that it would have been obvious to combine the teachings of Rundfeldt with respect to retigabine with the teachings of Cai, in view of the art cited in the instant specification, with regard to sodium channel blockers

to provide the presently claimed combination of retigabine and sodium channel blocker for the treatment of neuropathic pain.

With respect to Cai, Applicants respectfully disagree with the characterization of Cai as teaching "the routine knowledge in using sodium ion channel blocker [sic] such as riluzole, lidocaine, propafenone, and semicarbicarbazone derivatives for the treatment of neuropathic pain." In particular the following passage in Cai does not instill a sense of routine for *any* sodium channel blocker:

> "In addition to the above-mentioned clinical uses, carbamazepine, lidocaine and phenytoin are occasionally used to treat neuropathic pain,..." (col.1, lines 49-52)

Indeed, "occasionally" is used to qualify only those three drugs in particular, not sodium channel blockers as a whole as characterized by the Examiner. Furthermore, occasional use does not suggest routine use for these three drugs either. Moreover, on page 8 of the Office Action, the Examiner states that the "above references in combination make clear that retigabine and sodium channel blocker such as lidocaine, propageneone [sic], and riluzole have been individually used for treatment of neuropathic pain." In response, Applicants respectfully disagree with this characterization and point out that one skilled in the art will recognize that the use of *any* particular sodium channel blocker alone may fail to treat neuropathic pain for a number of reasons including, for example, (1) dose-limiting side effects (see for example the specification at page 5, lines 18-24) or (2) lack of bioavailability and/or short half-life (see for example, the specification at page 5, lines 24-31). Thus, in light of the teachings of the present specification, one skilled in the art would not be provided with an expectation of success in combining *any* sodium channel blocker with retigabine for the treatment of neuropathic pain as claimed. The present invention is based on the unexpected discovery of a synergism in the simultaneous use of a sodium channel blocker with a potassium channel opener, as exemplified by retigabine (see page 6, lines 27-33).

Thus, the Applicants claim to the combination of a sodium channel inhibitor with retigabine for the treatment of neuropathic pain is not obvious as a "combination of active ingredient with the same character" with "merely the additive effect of each individual component," as suggested by the Examiner (Office Action at page 8, first full paragraph).

Without addressing the merits of the Examiner's discussion of dosage forms, administration regimens, or specific types of neuralgia or neuropathic pain, including increase in muscle tone, which relate to various dependent claims, Applicants assert that independent claim 12 (and 15) are not obvious over Rundfeldt in view of Cai, and in further view of art cited in the background of the present specification. The claims dependent from claims 12 (and 15) are patentable for at least the same reasons. Applicants respectfully request withdrawal of this rejection.

The Examiner has separately rejected claims 14 and 15 under 35 U.S.C. §103(a) as allegedly being unpatentable over Rundfeldt et al. (U.S. 6,227,900) in view of Cai et al. (U.S. 6,281,211) and in further view of applicant's alleged admitted prior art of record (page 1, line 25- page 4, line 3). The Examiner argues that the alleged prior art of record teaches that tolperisone is a sodium channel blocker similar to lidocaine and would therefore behave in a similar manner and provide therapeutic utility through sodium channel blocking mechanism. With respect to claim 14, its dependence from claim 12 renders it patentable for at least the same reasons set forth above. With respect independent claim 15, Applicants point out that the specification teaches that tolperisone activity and duration of its effect is not satisfactory, stating possible reasons as lack of bioavailability and/or short half-life (specification at page 5, lines 24-31). Thus, the Examiner's association of tolperisone with lidocaine, with respect to the therapeutic utility through a sodium channel blocking mechanism, does not hold as a tenable argument regarding obviousness. Applicants respectfully request withdrawal of this rejection.

Finally, Applicants wish to clarify for the record the Examiner's response to the Applicants previously provided arguments. In particular, the Examiner appears to continue to mischaracterize Cai et al. as teaching that sodium channel blockers such as lidocaine, propafenone and riluzole have been used for the treatment of neuropathic pain. As exemplified by tolperisone discussed above, the property of being a sodium channel blocker alone is insufficient to constitute a viable mechanism to ensure successful treatment of neuropathic pain.

Entry of the proposed amendments is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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United States Patent [19]

Morita et al.

[11] **4,181,803**

[45] **Jan. 1, 1980**

[54] **PROPIOPHENONE DERIVATIVES AND PREPARATION THEREOF**

[75] Inventors: **Eiichi Morita; Takeo Kanai, both of Honjou, Japan**

[73] Assignee: **Eisai Co., Ltd., Tokyo, Japan**

[21] Appl. No.: **666,073**

[22] Filed: **Mar. 11, 1976**

Related U.S. Application Data

[63] Continuation of Ser. No. 530,499, Dec. 6, 1974, abandoned.

[30] **Foreign Application Priority Data**

Dec. 14, 1973 [JP] Japan 48-138808

[51] **Int. Cl.**[2] **C07D 295/10**

[52] **U.S. Cl.** **546/237; 424/267**

[58] **Field of Search** 546/237

[56] **References Cited**

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Porszasz et al., Chemical Abstracts, vol. 55 (1961) 13637a.

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Primary Examiner—Norma S. Milestone

Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] **ABSTRACT**

New propiophenone derivatives prepared by the reaction of propiophenone, formaldehyde and piperidine, as well as pharmacologically acceptable acid-addition salts thereof are provided, which possess improved pharmacological activities such as anti-tramorine and anti-nicotine activities superior to those of the known analoguous compound. The new compounds are useful for the therapeutic treatment of human patient suffering from pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like.

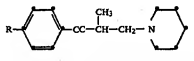
4 Claims, No Drawings

EXHIBIT A

PROPIOPHENONE DERIVATIVES AND PREPARATION THEREOF

This is a continuation, of application Ser. No. 530,499, filed Dec. 6, 1974 now abandoned.

This invention relates to the new amino-substituted propiophenone derivatives, that is, 4'-substituted 2-methyl-3-piperidino-propiophenones represented by the formula:



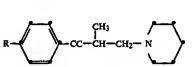
(I)

wherein R stands for a lower alkyl group having 2 to 3 carbon atoms, as well as pharmacologically acceptable acid-addition salts thereof, and a process for the preparation thereof.

It has been found that the new compounds of the present invention possess excellent anti-tremorine and anti-nicotine activities and thus useful for the therapeutic treatment of pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like. The compounds are also a prominant muscular relaxant for the stiffen muscle due to spinal polysynapse reflex-inhibiting action.

At present, 2,4'-dimethyl-3-piperidino-propiophenone hereafter called "Tolperisone" has been available in the market as the therapeutic agent clinically used for the treatment of spastic paralysis. The pharmacological activities of Tolperisone rely upon its spinal polysynapse reflex-inhibiting action and anti-tremorine and anti-nicotine activities.

As the result of thorough investigations effected by the present inventors for many years in order to discover another compound or compounds having therapeutic activities superior to those represented by Tolperisone, it has surprisingly been found that the new propiophenone derivatives represented by the formula:



(I)

wherein R stands for a lower alkyl group having 2 to 3 carbon atoms, are superior to Tolperisone with respect to their pharmacological activities. The performance of the present invention indeed relies upon said particular observations.

Accordingly, an object of this invention is to provide the novel therapeutic agent represented by the above-mentioned chemical formula (I) which is effective for the treatment of pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like.

Another object of the invention is to provide a novel muscular relaxant.

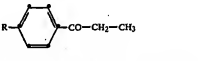
A further object of the invention is to provide a therapeutic agent having spinal polysynapse reflex-inhibitory activity, anti-tremorine and anti-nicotine activities and the like adaptable for the treatment of human patient suffering from pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like.

A still further object of the invention is to provide the novel propiophenone derivatives superior to Tolperisone with respect to the several pharmacological viewpoints.

A yet further object of the invention is to provide a process for the preparation of the abovementioned new therapeutic agent effective for the treatment of pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like.

It is also an object of the invention to provide a method for the therapeutic treatment of pathological muscular contracture, spastic paralysis due to cerebral apoplexy, spinal and cerebral palsies and the like.

The novel and useful propiophenone derivatives contemplated in the invention may be prepared by the process in which a ketonic compound, that is, 4'-substituted propiophenone represented by the formula:



(II)

wherein R stands for a lower alkyl group having 2 to 3 carbon atoms, is caused to reaction with formaldehyde and piperidine.

Although the abovementioned chemical reaction can be effected by suitably warming a mixture of the above-mentioned starting materials even in the absence of a reaction medium, it has been found that use of a suitable solvent is preferable and convenient for facilitating a finishing or working-up operation of the reaction product. Any conventional solvent may be employed for this purpose, and above all, lower alcohols such as methanol, ethanol, propanol and isopropanol are particularly mentioned therefor.

As to the formaldehyde as one of the reactants, there may preferably be employed a 30% aqueous solution of formaldehyde, that is, formalin, or paraformaldehyde.

The compounds of the formula (I) supra obtained by the process of the invention, if necessary, may be converted into their pharmacologically acceptable acid-addition salts by means of a conventional method. As exemplification of such acid-addition salts, there may be mentioned those of inorganic acids such as hydrochloric, hydrobromic, sulfuric and the like acids as well as those of organic acids such as acetic, maleic, fumaric, citric, succinic, oxalic, methanesulfonic and the like acids.

Excellent pharmacological activities represented by the compounds of the present invention are shown by the following experiments in comparison with those of Tolperisone which as previously mentioned has hitherto been clinically employed.

EXPERIMENTS

(a) The compounds used for the tests:

(1) The compounds belonging to the present invention:

4'-ethyl-2-methyl-3-piperidino-propiophenone hydrochloride hereinafter-called "Compound A";

4'-n-propyl-2-methyl-3-piperidino-propiophenone hydrochloride hereinafter-called "Compound B"; and

4'-isopropyl-2-methyl-3-piperidino-propiophenone hydrochloride hereinafter-called "Compound C".

(2) The compounds used for control:

Tolperisone hydrochloride, i.e., 2,4'-dimethyl-3-piperidino-propiophenone hydrochloride hereinafter-called "Compound for control".

(b) Methods

Male d_1d-strain mice weighing 18 to 22 grs. were used for the experiments.

Groups of each 10 mice were treated orally and intraperitoneally with a wide range of doses of the abovementioned compounds or saline.

(1) Anti-tremorine activity:

Antagonistic effects on the tremorine-induced tremor were observed as follows:

Ten (10) minutes after the intraperitoneal injection of the individual compounds under test, on one hand, and 40 minutes after the oral administration of said individual compounds, on the other hand, 20 mg/kg of tremorine hydrochloride were subcutaneously injected to each group of the mice. The occurrence of tremor on the individually caged mice was visually observed 20 minutes after the tremorine-injection.

(2) Anti-nicotine and anti-physostigmine activities:

Antagonistic effects against the convulsive death of the mice caused by the injections of nicotine, on one hand, and physostigmine, on the other hand, were observed as follows:

Thirty (30) minutes after the intraperitoneal injection of the individual compounds under test, on one hand, and 60 minutes after the oral administration of said individual compounds, on the other hand, 4 mg/kg of nicotine tartrate, on one hand, and 0.5 mg/kg of physostigmine sulfate, on the other hand, were intravenously injected to each group of the mice. The convulsive death, if any, of the mice in each group was then observed.

(3) Other activities:

Following the oral administration of the individual compounds under test, changes in the gross behaviors of the mice were observed in particular with respect to the motor function and the maintenance of righting reflex.

The mortality ensued during 24 hours after the oral administration was recorded to determine acute toxicity of the compound under test on the mice.

Additionally, anti-histamine, anti-acetylcholine, anti-serotonin and smooth muscle-relaxing activities of the compounds under test were examined on isolated smooth muscle preparations

(c) Results:

The numerals given in the following Table 1 indicate ED_{50} values (in mg/kg) which were calculated 60 minutes after the oral administration of the compounds under test.

Table 1

	Compounds under Tests			Compound for
	A	B	C	Control
Anti-tremorine activity	32	50	118	210
Anti-nicotine activity	175	135	37	450
Anti-Physostigmine activity	84	150	50	400[1] <
Motor Ataxia	640	800	84	800
Acute toxicity (24 hours)	800-	1000-	400-	1000-

Table 1-continued

	Compounds under Tests			Compound for
	A	B	C	Control
	1000	1500	500	1500

[1]No effect up to the dose.

The numerals given in the following Table 2 indicate ED_{50} values obtained from the result at the time of 30 minutes after the intraperitoneal injection of the individual compounds under test.

Table 2

	Compounds under test			Compound for
	A	B	C	Control
Anti-tremorine activity	23	21	25	80
Anti-nicotine activity	21	20	10	35

As is evident from the data given in the abovementioned Table 1, the acute toxicity of Compound B is almost equivalent to that of Compound under control. The acute toxicity of Compound A, on the other hand, is slightly stronger and the acute toxicity of Compound C is 2 to 3 times stronger than that of Compound under control.

Contrary to the above criticism on the toxicity, Compounds A, B and C, as is apparent from the data given in Tables 1 and 2, possess the pharmacological activities far stronger than those of Compound under control. More precisely, Compounds A, B and C were 2 to 7 times more potent than Compound under control on the anti-tremorine activity; 3 to 12 times more potent than Compound under control on the anti-nicotine activity; and 2 to 8 times more potent than Compound under control on the anti-physostigmine activity, all in the case of oral administration.

In like manner, Compounds A, B and C were 2 to 4 times more potent than Compound under control in the anti-tremorine and anti-nicotine activities, in the case of intraperitoneal administration.

In the further experiments on the isolated smooth muscle preparations, Compound under control produced a weak smooth muscle-relaxant activity in a potency of about $\frac{1}{3}$ times as compared with that exhibited by papaverine.

In contrast, it is notable, too, that Compound A with 4×10^{-6} g/ml, Compound B with 10^{-6} g/ml and Compound C with 4×10^{-7} g/ml in the respective concentrations that do not entirely produce anti-histamine and anti-acetylcholine activities, exhibited the strong smooth muscle-relaxant activities. The marked relaxant activities produced by Compounds A, B and C indeed are 2 to 3 times over the corresponding activity represented by papaverine and 3 to 10 times over the corresponding activity of Compound under control.

(d) Summary:

In viewpoint of the abovementioned pharmacological activities, it is obvious that the propiophenone derivatives specified in the present invention are superior to Compound under control, for example.

Accordingly, the specified propiophenone derivatives of the present invention are useful for the treatment of patients suffering from diseases such as muscular contracture, spastic paralysis, motor-disfunctions due to cerebral apoplexy, spinal and cerebral palsies, Parkinsonism and peripheral and cerebral vascular dis-

orders, stiffness of shoulder due to hypertension and the like.

Following Examples will serve to illustrate the embodiments of the production of the compounds contemplated in the invention, but the invention, of course, is not intended to be limited thereby.

EXAMPLE 1

Preparation of
4'-ethyl-2-methyl-3-piperidino-propiophenone

To 60 mls. of isopropanol, there are introduced 120 grs. of 4-ethyl-propiophenone, 28.8 grs. of paraformaldehyde and 107 grs. of piperidine hydrochloride, and the resulting mixture is heated to reflux on an oil bath with stirring. The heating is continued, and when the reaction mixture solidifies, the state being a sign of completion of the reaction, there are added 500 mls. of acetone thereinto. The solidified mass is pulverized by crush, recovered by filtration and washed with acetone. 144 Grs. of the crude crystalline substance are thus obtained which are the hydrochloride of the purposed product. The hydrochloride is recrystallized from isopropanol, and there are obtained the crystalline needles having the melting point of 170°–172° C.

Elementary analysis of the product presumed as $C_{17}H_{25}NO.HCl$ gives:

	C	H	N
Calculated (%):	69.00	8.87	4.73
Found (%):	68.99	8.92	4.59

EXAMPLE 2

Preparation of 4'-isopropyl-2-methyl-3-piperidino-propiophenone

To 350 mls. of isopropanol, there are introduced 350 grs. of 4-isopropyl-propiophenone, 270 grs. of a 30% aqueous formaldehyde and 266 grs. of piperidine hydrochloride together with 5 mls. of concentrated hydrochloric acid. The resulting mixture is heated to reflux on an oil bath with stirring for three hours. 500 mls. of acetone are then added to the reaction mixture with stirring. Crystals separate out from the reaction mixture are recovered by filtration and washed with acetone. There is thus obtained the crude hydrochloride of the purposed product in a crystalline form. The yield of the product amounts to 440 grs. The product is recrystallized from isopropanol and shows the melting point of 172°–174° C.

Elementary analysis of the product presumed as $C_{18}H_{27}NO.HCl$ gives:

	C	H	N
Calculated (%):	69.75	9.12	4.52
Found (%):	69.86	9.21	4.29

EXAMPLE 3

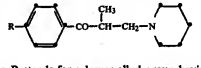
A compound depicted in the following Table is prepared in accordance with the procedure disclosed in Example 1.

Table

		Elementary Analysis Calculated (%) (Found) (%)		
	Molecular Formula			
R	(Melting Point)	C	H	N
$-CH_2CH_2CH_3$	$C_{18}H_{27}NO$. HCl	69.75	9.12	4.52
	(168°–169° C.)	(69.40)	(9.21)	(4.43)

What is claimed is:

1. A 4'-Substituted 2-methyl-3-piperidino-propiophenone derivative represented by the formula:



wherein R stands for a lower alkyl group having 2–3 carbon atoms or a pharmacologically acceptable acid-addition salt thereof.

2. A 4'-substituted-2-methyl-3-piperidino-propiophenone derivative according to claim 1 wherein the derivative is 4'-ethyl-2-methyl-3-piperidino-propiophenone or a pharmacologically acceptable acid-addition salt thereof.

3. A 4'-substituted-2-methyl-3-piperidino-propiophenone derivative according to claim 1 wherein the derivative is 4'-n-propyl-2-methyl-3-piperidino-propiophenone or a pharmacologically acceptable salt thereof.

4. A 4'-substituted-2-methyl-3-piperidino-propiophenone derivative according to claim 1 wherein the derivative is 4'-isopropyl-2-methyl-3-piperidino-propiophenone or a pharmacologically acceptable salt thereof.

* * * * *

United States Patent [19]

Uno et al.

[11] Patent Number: 4,528,299

[45] Date of Patent: Jul. 9, 1985

[54] 1-(2,3-DIMETHYL-4-METHOXYPHENYL)-2-METHYL-3-(1-PYRROLIDINYL)-1-PROPANONE AND ANTI-SPASTIC USE THEREOF

[75] Inventors: Hitoshi Uno, Takatsuki; Tadahiko Karasawa, Toyonaka; Tatsuya Kon, Ashiya; Tsugutaka Ito, Suita, all of Japan

[73] Assignee: Dainippon Pharmaceutical Co., Ltd., Osaka, Japan

[21] Appl. No.: 530,096

[22] Filed: Sep. 7, 1983

[30] Foreign Application Priority Data

Sep. 7, 1982 [JP] Japan 57-156081

[51] Int. Cl.³ C07D 207/04; A61K 31/40

[52] U.S. Cl. 514/428; 548/551

[58] Field of Search 548/551; 424/274

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Primary Examiner—Glennon H. Hollrah
Assistant Examiner—D. B. Springer
Attorney, Agent, or Firm—Wegner & Bretschneider

[57] ABSTRACT

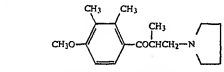
1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone and its pharmaceutically acceptable acid addition salts, which are useful as centrally acting muscle relaxants in the treatment of spasticity in mammals including humans, process for the preparation thereof, and pharmaceutical composition containing said compound as an active ingredient.

10 Claims, No Drawings

EXHIBIT B

1-(2,3-DIMETHYL-4-METHOXYPHENYL)-2-METHYL-3-(1-PYRROLIDINYL)-1-PROPANONE AND ANTI-SPASTIC USE THEREOF

The present invention relates to a novel 1-phenyl-2-methyl-3-(1-pyrrolidinyl)-1-propanone derivative which has central muscle relaxant activity and other pharmacological activities and hence is useful as a medicine. More particularly, it relates to 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone of the formula:



(I)

and a pharmaceutically acceptable acid addition salt thereof, a process for the preparation thereof, a method of use of said compound as a medicine, and a pharmaceutical composition containing said compound as an active ingredient.

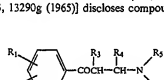
The pharmaceutically acceptable acid addition salts of the compound (I) include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, etc., and organic acid salts such as formate, acetate, citrate, maleate, fumarate, tartrate, benzoate, lactate, methanesulfonate, etc.

There have hitherto been known various 1-phenyl-3-amino-1-propanone derivatives, for example, the following compounds.

It is known that 2-methyl-1-p-methylphenyl-3-piperidino-1-propanone (generic name: tolperisone) is useful as a centrally acting muscle relaxant [cf. Merck Index, 9th ed., 9219 (1976)]

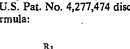
It is disclosed in U.S. Pat. Nos. 3,995,047 and 4,181,803 that 1-p-C_{2-3} alkylphenyl-2-methyl-3-piperidino-1-propanone shows improved pharmacological activities superior to those of tolperisone.

Japanese Patent Publication No. 11,490/1965 [Chem. Abstr., 63, 13290g (1965)] discloses compounds of the formula:



wherein R_1 and R_2 are the same or different and are each halogen atom or alkyl group, R_3 and R_4 are the same or different and are each a hydrogen atom or alkyl group, and R_5 and R_6 are the same or different and are each a hydrogen atom, aliphatic group, or combine together with the adjacent nitrogen atom to form a ring, which have an antispasmodic activity.

Furthermore, U.S. Pat. No. 4,277,474 discloses compounds of the formula:



wherein A is a non-substituted aryl group or aryl group substituted by a hydroxy group, lower alkyl group, lower alkoxy group, aryl group or a halogen, or non-substituted benzo[b]thienyl group or benzo[b]thienyl group substituted by hydroxy group, lower alkyl group, lower alkoxy group, aryl group or halogen, B is a di-lower alkylamino group or heterocyclic group which contains at least one nitrogen atom and may be substituted by a lower alkyl group or aralkyl group; however, when A is p-methylphenyl group, B denotes a group other than piperidino group, and R_1 is hydrogen, lower alkyl group or aryl group, or a pharmaceutically acceptable salt thereof, which are useful for treating allergic diseases.

The neurological disorders frequently seen in elderly men are hemiplegia or hemiparesis resulting from cerebral hemorrhage or infarction, muscle spasm, painful shoulder syndromes, low back pain, and the like. These are characterized mainly by hyperreflexia and hypertonia of the muscle, the so-called spasticity. The spasticity also occurs in brain and spinal cord injury and is frequently observed in cerebral palsy, multiple sclerosis and other neuronal disorders. For the treatment of these spastic syndromes, centrally acting muscle relaxants such as tolperisone have been prescribed. However, tolperisone seems to have some drawbacks such as insufficient potency and short duration of actions.

Under the circumstances, the present inventors have intensively studied an improved centrally acting muscle relaxant having potent and prolonged activity. As a result, it has been found that the compound of the formula (I) and a pharmaceutically acceptable acid addition salt thereof show the desired excellent activities.

An object of the present invention is to provide a novel 1-phenyl-2-methyl-3-(1-pyrrolidinyl)-1-propanone derivative which has excellent central muscle relaxant activity. Another object of the invention is to provide a process for the preparation of said compound. A further object of the invention is to provide a pharmaceutical composition containing said compound as an active ingredient which is useful for the treatment of spasticity in mammals including humans. Still further object of the invention is to provide use of said compound for the treatment of spasticity as set forth above. These and other objects and advantages of the invention will be apparent to persons skilled in the art from the following description.

The compound of the formula (I) can be prepared, for example, by reacting 1-(2,3-dimethyl-4-methoxyphenyl)-1-propanone with formaldehyde and pyrrolidine or an acid addition salt thereof. This reaction may be carried out without using any solvent, but is preferably carried out in an appropriate solvent in view of easy operation after the reaction. The solvent includes all solvents which are usually used in a Mannich reaction, for example, lower alcohols (e.g. methanol, ethanol, propanol, isopropanol), aromatic hydrocarbons (e.g. benzene, toluene), ethers (e.g. 1,2-dimethoxyethane), nitroalkanes (e.g. nitromethane), acetonitrile, and a mixture of these solvents. Formaldehyde and pyrrolidine are usually used in an amount of one to about three moles per one mole of 1-(2,3-dimethyl-4-methoxyphenyl)-1-propanone. Formaldehyde may be used in the form of formalin or a polymerized substance such as paraformaldehyde or s-trioxane. The reaction is usually carried out at a temperature of from room temperature to about 130° C. for about 0.5 to 48 hours.

The compound (I) can be isolated from the reaction mixture and purified by conventional methods. According to conditions of the reaction and after-treatment thereof, the compound (I) can be obtained in the form of

a free base or an acid addition salt. When the compound (I) is obtained in the form of an acid addition salt, it can easily be converted into a free base by treating it with a base such as an alkali metal carbonate or ammonia in a usual manner. On the other hand, when the compound is obtained in the form of a free base, it can easily be converted into an acid addition salt by treating it with an inorganic or organic acid in a usual manner.

The starting 1-(2,3-dimethyl-4-methoxyphenyl)-1-propanone used in the above reaction is also novel and can be prepared by the method as described in reference example hereinafter.

The pharmacological activities of the compound (I) of the present invention were experimented in comparison with those of known and novel compounds which have a chemical structure similar to that of the present compound (I). The test compounds are shown in Table 1, wherein the compounds 6 to 8 are all novel and are newly prepared by the present inventors.

TABLE 1

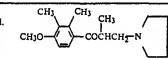
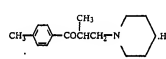
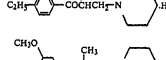
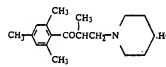
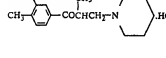
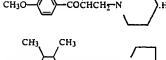
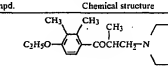
Test compd.	Chemical structure	Note
A (compd. of the present invention) (Ref. compd.)		
1		tol-perisone hydro-chloride
2		U.S. Pat. Nos. 3995047 and 4181803
3		U.S. Pat. No. 4277474
4		U.S. Pat. No. 4277474
5		Jap. Pat. Pub. No. 11490/1965 U.S. Pat. No. 4277474
6		Melting point 170-171° C.
7		Melting point 167-172° C.

TABLE 1-continued

Test compd.	Chemical structure	Note
8		Melting point 181-183° C.

TEST 1

Effect on anemic decerebrate rigidity (α-rigidity)

Anemic decerebrate rigidity is known to be a model showing the abnormal hypertonia. This model was prepared according to the method of Fukuda et al [cf. Japan. J. Pharmacol. 24, 810-813 (1974)]. Male rats of Wistar strain, weighing 250 to 350 g, were used in groups of 5 animals. Under the ether anesthesia, the animal was fixed on its back. After the oesophagus and bilateral common carotid arteries were exposed, the trachea was cannulated and the oesophagus was cut between two placed ligatures. The occipital bone was exposed. The common carotid arteries were ligated bilaterally and a trephined opening was made in the central part of the bone. The dura matter was cut along the basilar artery, and the artery was cauterized with a coagulator of bipolar pincette electrodes (Micro-ID made by Mizuhoika Kogyo Co., Ltd., Japan). After the operation, anesthesia was discontinued. The marked rigidity occurred in the forelimbs within 15 minutes after the operation.

The rat was placed on its back and the hindlimbs fixed. Electromyogram (EMG) was recorded by a coaxial needle electrode inserted into the Musculus triceps brachii of the forelimbs. Reference electrode was inserted into the hindlimb muscle. EMG activities obtained from the muscle were amplified, transformed into the square wave pulses with the window discriminator, and fed into integrator, the out-put of which was amplified and recorded by an inkwriting recorder.

The test compounds were dissolved in distilled water. After the EMG activities had remained stable over 15 to 30 minutes, the test compounds were cumulatively injected at a 5-minute interval into a cannulated femoral vein. The doses administered were 1.25 mg/kg, 2.5 mg/kg, 5.0 mg/kg, 10 mg/kg and finally 20 mg/kg. The EMG activities were expressed as a percentage of the pre-injection value, and the maximal effect within 5 minutes was measured in each dose. The median effective dose (ED_{50}), the dose which reduced the EMG activity to 50%, was calculated by the method of Litchfield and Wilcoxon. In addition, the time from disappearance to reappearance of EMG activities after total dose of 20 mg/kg was expressed as the duration of the effect.

TEST 2

Muscle relaxant effect (Traction test)

Traction test was used as an index of the muscle relaxation. Male mice of STD-ddY strain, weighing 20 to 25 g, were used in groups of 5 animals. The test compounds, suspended or dissolved in 0.5% tragacanth solution, were intraperitoneally administered at a volume of 0.1 ml/10 g body weight, and 15 minutes after the administration the muscle relaxant effects were examined according to the method of Courvoisier et al

(cf. "Psychotropic Drugs", ed. by Garattini, S. and Ghetti, V., Elsevier Pub. Co., Amsterdam, 1957, page 373). The animal was suspended by their forelimbs on a horizontal metal bar with a diameter of 2 mm. The rod was 18 cm above the floor. The animals which could not put their hindlimb on the rod within 5 seconds were judged as a positive (all-or-nothing way). The median effective dose (ED_{50}), the dose which caused the positive effects in 50% of animals, were calculated according to the method of Litchfield and Wilcoxon.

TEST 3

Acute toxicity

Male mice of STD-ddY strain, weighing 23 to 25 g, were used in groups of 10 animals. The test compounds, suspended or dissolved in 0.5% tragacanth solution, were intraperitoneally administered at a volume of 0.1 ml/10 g body weight. After the administration, the mice were kept for 7 days, and observed for death. The median lethal dose (LD_{50}), the dose which caused death in 50% of animals, were calculated according to the method of Litchfield and Wilcoxon.

The results of the Tests 1, 2 and 3 are shown in Table 2.

TABLE 2

Test compound	α-Rigidity reducing effect: ED_{50} (mg/kg, i.v.)	Duration (minute)	Muscle relaxant effect: ED_{50} (mg/kg, i.p.)	Acute toxicity: LD_{50} (mg/kg, i.p.)	Safety*1 index
A	2.6	16.3	68.5	160.9	2.35
1	12.3	0.7	156.3	210.1	1.34
2	12.7	2.8	64.2	128.8	2.01
3	20.2	—*2	158.2	246.7	1.56
4	6.9	—*3	122.8	156.4	1.27
5	15.6	8.8	59.3	139.9	2.36
6	7.3	11.4	77.7	145.2	1.87
7	17.2	—*2	87.1	174.5	2.00
8	9.6	14.8	75.5	134.5	1.78

[Remarks]:
*1(LD_{50})/(ED_{50} of Muscle relaxant effect)
*2Not determined due to incomplete suppression of EMG activity at 20 mg/kg total dose.
*3Not determined due to the death of animals.

From the experimental results shown in Table 2, the following points are clear.

(i) The compound of the present invention is about 4.7 times as potent as Compound No. 1 in the reducing activity of α-rigidity and also about 23 times as long as the latter in the duration of action, and further about 2.3 times as potent as the latter in the muscle relaxant activity. The safety index of Compound No. 1 is so low as 1.34, but on the other hand, the compound of the present invention shows such a high safety index as 2.35, which is about 1.8 times that of Compound No. 1.

(ii) The compound of the present invention is about 4.9 times as potent as Compound No. 2 in the reducing activity of α-rigidity and also about 5.8 times as long as the latter in the duration of action.

(iii) The compound of the present invention is about 7.8 and 2.3 times as potent as Compound No. 3 in α-rigidity reducing and muscle relaxant activities, respectively. The safety index of the compound of the present invention is about 1.5 times that of Compound No. 3.

(iv) The compound of the present invention is about 2.7 and 1.8 times a potent as Compound No. 4 in α-rigidity reducing and muscle relaxant activities, respectively. Compound No. 4 has such a very low safety index as 1.27 and further shows high toxicity in rats.

(v) The compound of the present invention is about 6 times as potent as Compound No. 5 in the reducing activity of α-rigidity and also about 1.9 times as long as the latter in the duration of action.

(vi) The compound of the present invention is about 2.8 times as potent as Compound No. 6, which is merely different from the compound of the present invention in that it has piperidino group instead of 1-pyrrolidinyl group at 3-position, in the reducing activity of α-rigidity and also somewhat longer than the latter in the duration of action. Besides, the compound of the present invention has a higher safety index than that of Compound No. 6.

(vii) The compound of the present invention is about 6.6 times as potent as Compound No. 7, which is merely different from the compound of the present invention in that it has hydrogen atom instead of methyl group at 2-position, in the reducing activity of α-rigidity.

(viii) The compound of the present invention is about 3.7 times as potent as Compound No. 8, which is merely different from the compound of the present invention in that it has ethoxy group instead of methoxy group at paraposition of 1-phenyl group, in the reducing activity of α-rigidity. Besides, the compound of the present invention has a higher safety index than that of Compound No. 8.

Thus, the compound of the present invention has far greater pharmacological activities than known analogous compound Nos. 1 to 5 and has also fairly or far greater pharmacological activities than novel analogous compound Nos. 6 to 8.

As is clear from the above explanation, the compound (I) or its pharmaceutically acceptable acid addition salts have highly improved, excellent central muscle relaxant activities in comparison with the known compounds and also show low toxicity. Accordingly, the compound of the present invention is useful as a centrally acting muscle relaxant for the treatment of the spasticity in mammals including humans which is observed in the diseases such as cerebral hemorrhage or infraction, brain and spinal cord injury, cerebral palsy, multiple sclerosis, trauma, intervertebral disc herniation, painful shoulder syndromes, low back pain, postoperative joint pain, and the like.

The compound (I) and pharmaceutically acceptable acid addition salt thereof can be administered in oral, parenteral or intrarectal route, preferably in oral route. The dose of these compounds varies with the administration routes, the age of the patients, the kinds and severity of the diseases to be treated, or the like, but is in the range of 0.5 to 20 mg, preferably 0.6 to 6 mg, as the free base per kg of body weight per day for humans. The dose may be divided and administered in two to four times per day.

The compound (I) and pharmaceutically acceptable acid addition salts thereof are usually administered to patients in the form of a pharmaceutical composition which contains a non-toxic and effective amount of the compounds. The pharmaceutical composition is usually prepared by admixing the active compound (I) or its salt with conventional pharmaceutical carrier materials which are unreactive with the active compound (I) or its salts. Suitable examples of the carrier materials are lactose, glucose, mannitol, dextran, cyclodextrin, starch, sucrose, magnesium aluminosilicate tetrahydrate, synthetic aluminum silicate, microcrystalline cel-

lulose, sodium carboxymethylcellulose, hydroxypropylstarch, calcium carboxymethylcellulose, ion exchange resin, methylcellulose, gelatin, acacia, hydroxypropylcellulose, low substituted hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, light anhydrous silicic acid, magnesium stearate, talc, tragacanth, bentonite, veegum, carboxyvinyl polymer, titanium dioxide, sorbitan fatty acid ester, sodium lauryl sulfate, cacao butter, glycerin, glycerides of saturated fatty acids, anhydrous lanolin, glycerogelatin, polysorbate, macrogol, vegetable oils, wax, propylene glycol, water, or the like.

The pharmaceutical composition may be in the dosage form of tablets, capsules, granules, fine granules, powders, syrups, suspension, suppositories, injections, or the like. These preparations may be prepared by conventional methods. Liquid preparations may be prepared by dissolving or suspending the active compounds in water or other suitable vehicles, when used. Tablets, granules or fine granules may be coated in a conventional manner.

The pharmaceutical composition may contain as the active ingredient the compound (I) or its pharmaceutically acceptable acid addition salt in the ratio of 0.5% by weight or more, preferably 1 to 70% by weight, based upon the whole weight of the compositions. The composition may further contain one or more other therapeutically active compounds.

The present invention is illustrated more specifically by the following Examples and Reference Examples. It should be understood that the invention is not limited to these examples.

EXAMPLE 1

1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride

1-(2,3-Dimethyl-4-methoxyphenyl)-1-propanone (20.0 g), paraformaldehyde (6.2 g) and pyrrolidine (8.9 g) are combined in isopropanol (30 ml) and 35% ethanolic hydrogen chloride (16 ml) is added to adjust the solution to an acidic pH. The mixture is then stirred and heated at reflux for 20 hours. After cooling, acetone (300 ml) is added to the reaction mixture and the resulting solution is cooled in ice water. Crystalline product is filtered and recrystallized twice from ethanol (50 ml)-acetone (50 ml) to give the analytically pure title compound (10.0 g), m.p. 169°-172° C.

Analysis-Calcd. for $C_{17}H_{25}NO_2$.HCl: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.23; H, 8.43; N, 4.64; Cl, 11.67.

EXAMPLE 2

1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3(1-pyrrolidinyl)-1-propanone and its hydrochloride

1-(2,3-Dimethyl-4-methoxyphenyl)-1-propanone (50.0 g), paraformaldehyde (15.6 g) and pyrrolidine (22.0 g) are combined in acetonitrile (250 ml) and 34% isopropanolic hydrogen chloride (38 ml) is added to adjust the solution to an acidic pH. The mixture is then stirred and heated at reflux for 6.5 hours. After cooling in ice water, crystalline product is filtered and washed with cold acetone. Recrystallization twice from ethanol (150 ml)-acetone (150 ml) gives the analytically pure hydrochloride of the title compound (38.0 g), m.p. 172°-176° C.

Analysis-Calcd. for $C_{17}H_{25}NO_2$.HCl: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.25; H, 8.25; N, 4.48; Cl, 11.44.

The hydrochloride thus obtained (10.0 g) is added to a solution of potassium carbonate (5.3 g) in water (50 ml) and an oily substance separated is extracted twice with n-hexane (25 ml). The combined n-hexane layers are washed twice with water and dried over anhydrous sodium sulfate. The solvent is distilled off to give the free base of the title compound (7.7 g).

PMR(CDCl$_3$)δ: 1.18 (3H, d, J=7 Hz), 2.18 (3H, s), 2.32 (3H, s), 3.85 (3H, s), 6.71 (1H, d, J=8 Hz), 7.42 (1H, d, J=8 Hz).

REFERENCE EXAMPLE

1-(2,3-Dimethyl-4-methoxyphenyl)-1-propanone

To a stirred solution of 2,3-dimethylanisole (197.0 g) and propionyl chloride (147.0 g) in carbon disulfide (700 ml) is added anhydrous aluminum chloride (232.0 g) at 5°-10° C. over a period of 1.5 hours. Stirring is continued for 2 hours under cooling and additional 3 hours at room temperature. The reaction mixture is poured onto crushed ice—concentrated hydrochloric acid with stirring. The mixture is extracted with chloroform and the chloroform solution is washed successively with water, dilute sodium bicarbonate solution and water and then dried over anhydrous sodium sulfate. After removal of the solvent by evaporation, the residue is distilled at 121°-126° C. (1-2 mmHg) to give the title compound (255.0 g), which is crystallized from n-hexane, m.p. 39°-40° C.

Analysis-Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.82; H, 8.36.

PMR(CDCl$_3$)δ: 1.17 (3H, t, J=7 Hz), 2.13 (3H, s), 2.35 (3H, s), 2.87 (2H, q, J=7 Hz), 3.83 (3H, s), 6.73 (1H, d, J=8 Hz), 7.47 (1H, d, J=8 Hz).

Example 3

	per 1,000 tablets
1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride	20 g
Corn starch	28 g
Lactose	65 g
Microcrystalline cellulose	30 g
Hydroxypropylcellulose	5 g
Light anhydrous silicic acid	1 g
Magnesium stearate	1 g

The above components are blended, granulated and made into 1,000 tablets each weighing 150 mg by a conventional method. The tablets are further coated with hydroxypropyl methylcellulose, talc, titanium dioxide, and sorbitan monooleate in a customary manner. There are obtained 1,000 film coated tablets.

Example 4

	per 1,000 capsules
1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propane hydrochloride	50 g
Corn starch	70 g
Lactose	56 g
Microcrystalline cellulose	40 g
Talc	2 g
Magnesium stearate	2 g

The above components are blended, granulated and filled into 1,000 capsules by a conventional method.

Example 5

	fine granules
1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride	100 g
Corn starch	200 g
Lactose	660 g
Light anhydrous silicic acid	10 g
Hydroxypropylcellulose	30 g

The above components are blended and made into fine granules by a conventional method. The fine granules are further coated with dimethylaminoethyl acrylate-methacrylate copolymer, macrogol aand maagnesium stearate.

What is claimed is:

1. 1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone or a pharmaceutically acceptable acid addition salt thereof.

2. 1-(2,3-Dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride.

3. A pharmaceutical composition comprising as an active ingredient an effective antispastic amount of 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 4 wherein the active ingredient is 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride.

5. A method of treating spasticity in mammals which comprises administering to said mammals in need of such treatment an effective antispastic amount of 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone or a pharmaceutically acceptable acid addition salt thereof.

6. The method of claim 5 wherein said compound is 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride.

7. The method of claim 5 wherein said compound is administered in a daily dosage of from 0.5 to 20 mg per kg of body weight as the free base.

8. The method of claim 7 wherein said compound is 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride.

9. The method of claim 7 wherein said daily dosage is in the range of 0.6 to 6 mg per kg of body weight as the free base.

10. The method of claim 9 wherein said compound is 1-(2,3-dimethyl-4-methoxyphenyl)-2-methyl-3-(1-pyrrolidinyl)-1-propanone hydrochloride.

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